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Title: **Applying inline spatial filter velocimetry to improve process robustness of a continuous twin-screw wet granulator**

Within the pharmaceutical manufacturing industry there is a necessary trend towards improved process understanding. This includes having fundamental knowledge of the various mechanisms taking place as well as improved measurements and data analysis. The main purpose of this knowledge expansion is to improve design and operation of the various unit operations. This way, robust processes are established which minimize output variability resulting from uncontrolled process disturbances.

Clearly, real-time measurement instrumentation can facilitate in bridging the current knowledge gaps by providing rapid screening for process development as well as routine monitoring of product variability. With respect to granulation, precise inline measurement of granule characteristics (e.g. size, content uniformity and bulk density) is seen as an attractive solution to ensure robust production of oral solid dosage forms.

This work exemplifies the application of inline particle size analysis based on spatial filter velocimetry (Parsum IPP 70, Malvern Instruments Ltd, United Kingdom) for continuous twin-screw wet granulation line, ConsiGmaTM-25 (GEA Pharma Systems, Belgium). Initial experimentation revealed that the measurement capability of the instrument depends predominantly on the interfacing in the actual process stream. Multiple design iterations lead to a satisfying measurement system for real-time granule size analysis.

The instrument together with its interfacing was subsequently used to evaluate different strategies to operate and control the manufacturing of pharmaceutical granules through continuous wet granulation. To this end, different descriptors derived from the measured number and volume based size distributions (i.e. median, span, moments and mean diameters) were assessed with respect to their sensitivity under dynamic process conditions. Indeed, (un)intended dynamic changes to the process were correctly identified using the proposed measurement system. However, there exists a fine balance between the accuracy of the measurement system and the detection speed of granule size changes. A more feasible approach exists in complementing inline size measurements with instrument metadata (i.e. particle rate and loading) together with univariate process measurements (i.e. torque) into one multivariate framework. This way, a fast and reproducible method to identify unintended output variability can be established.

Besides pure data-driven monitoring, the combination of mathematical modelling together with inline size analysis could result in a powerful solution for automatic size control of twin-screw wet granulation processes. Therefore, some initial work will also be presented on the comparison of an existing population balance model and measurements obtained from inline spatial filter velocimetry.